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ORIGINAL ARTICLE

Dosage and duration of antipsychotic treatment in demented outpatients with agitation or psychosis

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Background/Purpose: The USA Food and Drug Administration (FDA) issued warnings regarding the use of antipsychotics in patients with dementia in 2003 and 2005. We aimed to study the dose and duration of antipsychotic treatment in dementia, and to examine whether physicians' prescription behaviors changed after the FDA warnings.
Methods: Medical charts of outpatients who had Alzheimer's disease, vascular dementia, or mixed dementia were reviewed. Patients must have achieved a clinically stable state for at least 4 weeks after receiving antipsychotic treatment for agitation or psychosis. Demographics, clinical correlates, and duration of antipsychotic treatment were compared among different antipsychotic groups. Because the quetiapine group had the largest sample size, the optimal dose and duration of quetiapine treatment were compared among three time periods (before 2003, 2003–2005, after 2005).
Results: Stable state was achieved in 215 patients (80 had Alzheimer's disease, 117 vascular dementia, and 18 mixed dementia). Most patients (177) took quetiapine, 25 took risperidone, and 13 took sulpiride. The whole sample had a long total duration of antipsychotic treatment

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(median 525 days, mean 707 days). The median dose and total duration of antipsychotic treatment were 1.0 mg/day and 238 days for risperidone, 100 mg/day and 390 days for sulpiride, and 25 mg/day and 611 days for quetiapine, respectively. The optimal dose and total duration of quetiapine treatment decreased significantly after FDA warning in 2005, although the duration remained long. *Conclusion:* The optimal doses of antipsychotics were not higher than those of western reports, but the total duration of antipsychotic treatment was quite long. Although our study suggests the prescription dosage and duration of antipsychotic treatment decreased significantly after FDA warning in 2005, the duration of treatment was still long. Given the serious safety concerns, more effort should be made to avoid unnecessary and prolonged prescription.

Introduction

The prevalence of dementia increases with age, and it was estimated that 24.3 million people had dementia worldwide in 2005 and the number will double every 20 years, reaching over 80 million by 2040.[1] Dementia is a deteriorating disorder accompanied with various distressing neuropsychiatric symptoms. During the course of Alzheimer's disease (AD), up to 90% of patients develop the behavioral and psychological symptoms of dementia, of which psychosis and agitation present in more than half of all patients.[2–4] Furthermore, dementia-related psychosis and agitation have been reported to be associated with decreased quality of life,[5] more rapid cognitive decline,[6] increased burden on caregivers,[7] early institutionalization,[8] and even higher mortality.[9,10]

Although no pharmacotherapy has been approved by the US Food and Drug Administration (FDA) for patients with dementia-related agitation or psychosis, off-label use of antipsychotic agents is common. Before 2005, antipsychotic agents were recommended as the first-line pharmacotherapy for agitated dementia with delusions and as the high-second line for agitated dementia without delusions.[11] Atypical antipsychotic agents are preferred over typical antipsychotic agents as they have fewer extrapyramidal side effects. Many clinical trials revealed a better efficacy for antipsychotic agents as compared with placebo, but there were also inconsistent results. A meta-analysis of 15 placebo-controlled, double-blind, parallel-group trials involving four atypical antipsychotic agents showed only modest efficacy on rating scales for risperidone and aripiprazole, but not for olanzapine.[12] Another meta-analysis focusing on aggression and psychosis in AD showed significant improvements in aggression with risperidone and olanzapine treatment, but only significant improvements in psychosis with risperidone treatment.[13] Unfortunately, antipsychotic agents were noted to be associated with increased risk for cerebrovascular accidents in elderly demented patients, so the FDA issued a "Dear Healthcare Professional" letter in April 2003.[14] Further, meta-analysis found significantly increased mortality rate with 6- to 12-week atypical antipsychotic treatment in patients with dementia.[15] Therefore, in April 2005, the FDA issued a black box warning that antipsychotics could increase mortality risk in demented patients.[16] Considering both the efficacy and adverse effects, clinicians face a decision dilemma when treating patients with agitation or psychosis. Nonpharmacological interventions may be tried first, and when necessary, the lowest dosage and shortest duration of antipsychotic agent treatment are recommended. However, data about physicians' prescribing behaviors in real life practice are missing in Taiwan. Hence we conducted a study to investigate the dosage and duration of antipsychotic treatment in demented outpatients with agitation or psychosis. Specifically, we wanted to investigate: (1) the dosage and duration of antipsychotic treatment in demented outpatients with agitation or psychosis; and (2) whether the prescription behaviors changed after FDA warnings in 2003 and 2005.

Methods

Patients

This was a retrospective study using the chart review method. Elderly patients who were diagnosed as having dementia at neurology and psychiatric clinics were sampled in an exhaustive way according to predefined criteria in the National Taiwan University Hospital. In the first step, all candidate patients were selected from the hospital database if they had a diagnosis of dementia between January 2006 and December 2007. In the second step, patients' eligibility into this study was evaluated by four senior psychiatric residents knowledgeable in the diagnosis and management of dementia through chart review. To be included, each patient must meet five inclusion criteria: (1) diagnosis of AD, VaD, or mixed dementia by a neurologist or a psychiatrist; (2) a mini-mental status examination score between 10 and 26; (3) being prescribed an antipsychotic agent indicated solely for dementia-related agitation or psychosis at outpatient clinics; (4) not receiving any other antipsychotic agent previously or concurrently; and (5) having achieved a predefined "stable state" (definition below). The diagnosis of AD and VaD was based on DSM-IV-TR.[17] Mixed dementia was defined as cognitive decline sufficient to impair independent functioning in daily life resulting from the coexistence of AD and cerebrovascular pathology, documented either by clinical criteria or by neuroimaging findings.[18] Candidate patients were excluded if they had a diagnosis of a primary psychotic disorder, delirium, other dementias (such as Lewy body dementia) that warranted the use of antipsychotic agents, or other conditions (such as concurrent medical disease, medications, substance abuse) contributing to agitation or psychosis.

Definitions of stable state, optimal dose, time to stable state, duration of stable state, and total duration of antipsychotic treatment

Medical chart review was done between June 2008 and September 2008. "Stable state" was defined as the first period of time after initiation of antipsychotic treatment during which: (1) there had been at least two clinical visits at an interval of at least 4 weeks; (2) a constant dose of antipsychotic agent had been maintained throughout; and (3) clinical improvements were achieved and documented in the charts. A similar definition has been employed to study the optimal dose of antipsychotic treatment in schizophrenia.[19] This definition reflected both clinical efficacy and tolerability of treatment. The at-least-4-week duration is considered adequate since expert opinions recommend discontinuing or switching an antipsychotic agent after 2 to 4 weeks when patients are no longer benefiting from it.[11,20] A stable state ended when target antipsychotic agent was either discontinued, changed in dosage, or added with another antipsychotic agent to control symptoms. "Optimal dose" was defined as the constant dose of an antipsychotic agent during the stable state. "Time to stable state" was defined as the time elapsed from the initial prescription of target antipsychotic agent to the beginning of stable state. "Duration of stable state" was counted from the beginning to the end of stable state, or from the beginning to the time of chart review if patients had not left the stable state. Total duration of target antipsychotic treatment was counted from the beginning of the stable state to the time of discontinuation of target antipsychotic agent or the time of chart review, whichever came first. The main reason to adopt the definition of stable state was to examine clearly how long the antipsychotic agent was kept for a stabilized patient until different outcome (for example, psychotic symptoms ameliorated or aggravated).

In the sample, some patients might receive a diagnosis of dementia in the 1990s and were prescribed of an antipsychotic agent for dementia-related agitation/ psychosis in the 1990s too. Because the chart review time was between June 2008 and September 2008, these patients might have long duration of stable state and total duration of antipsychotic treatment if the antipsychotic agent was continuously prescribed.

Data extraction

The data of the enrolled patients were extracted through medical chart review by three senior psychiatric residents knowledgeable about dementia. Discussions were made for the first three to five charts reviewed by each resident to reach consensus and to ensure the quality and consistency of the review process. Eligibility of the recruited patients and correctness of the collected data were double checked by the fourth senior psychiatric resident (Y.T.L.). A geriatric psychiatry specialist (T.J.H.) supervised the whole work. If there were any doubt, the team would discuss to reach final consensus.

A total of 695 candidate dementia patients were retrieved from the hospital database, and 217 patients were eligible for final analysis. Of the 478 excluded patients, 130 were diagnosed for other dementia subtypes, 212 failed to achieve stable states, 69 had compromising medical conditions affecting the use of antipsychotic agents, 38 had other concurrent reasons contributing to behavioral symptoms, and the remaining 29 were excluded for other reasons, such as use of two antipsychotic agents or no dementia-related behavioral symptoms. There were no statistically significant differences on sex or age between the 217 included and 478 excluded patients (or 212 patients who failed to achieve stable state; $p > 0.10$).

Demographic data, dementia subtype, symptom profile and severity, concurrent medications, and smoking and alcohol use were recorded. Reviewers determined the stable state, optimal dose, time to stable state, and total duration of antipsychotic treatment. The severity of agitation and psychosis was defined as follows: "mild to moderate" referred to symptoms that usually could be calmed down by caregivers, but sometimes disturbing; "severe" indicated significant suicidal or violence risks, or conditions necessitated hospitalization; and "moderate to severe" stood for severity between the former 2 conditions. If the severity couldn't be judged, "unknown" severity was coded. The study was approved by the institutional review board of National Taiwan University Hospital.

Statistical methods

Enrolled patients were grouped by types of antipsychotic agents they took during stable states. Demographic data and clinical correlates were compared among groups by using Chi-square test (or Fisher exact test) for categorical variables and ANOVA for continuous variables. For time to stable state, duration of stable state and total duration of target antipsychotic treatment, Kruskal—Wallis test and Mann—Whitney test were used. Since the quetiapine group had the largest sample size, we used it to investigate whether there were changes on physicians' prescription behaviors before and after the FDA's warnings in 2003 and 2005. Thereafter we subdivided patients into three cohorts according to the starting points of target antipsychotic agents: Cohort 1: starting points before April 30, 2003; Cohort 2: starting points between May 1, 2003 and April 30, 2005; Cohort 3: starting points between May 1, 2005 and April 30, 2006. Since the chart review began around June 2008, each cohort could be observed and followed-up for 2 years. Duration of stable state and total duration of quetiapine treatment were counted and truncated to 2 years (i.e., the maximal value would be 730 days). Kruskal—Wallis test and Mann—Whitney test were used for comparison among and between groups. Because there were data of behavioral pathology in Alzheimer's disease (BEHAVE-AD) recorded in the charts for 25 patients at the time near the beginning of antipsychotic agent treatment, we used these data to examine the correlation between severity rating defined in this study and the global rating score of BEHAVE-AD (4-point scale, rated from 0—3) by Kendall's tau.

Results

A total of 217 patients had achieved stable state, and 215 of them comprised the three antipsychotic groups (Table 1).

Table 1 Demographic data and clinical correlates of three antipsychotic groups.

Characteristics	Total ($N = 215$)	Risperidone ($N = 25$)	Sulpiride ($N = 13$)	Quetiapine ($N = 177$)	χ^2 or F
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (y)	77.5 (8.1)	73.1 (10.1)‡	75.1 (6.3)	78.3 (7.7)	5.16†
Duration of illness (y)	2.8 (2.5)	2.9 (3.0)	1.7 (1.1)	2.9 (2.5)	1.36
Mini-mental status examination score	14.7 (6.5)	16.3 (6.8)	18.6 (4.3)	14.3 (6.4)	1.64
	N (%)	*N* (%)	*N* (%)	*N* (%)	
Sex (female)	128 (59.5)	11 (44.0)	7 (53.8)	110 (62.1)	3.18
>9 y of education	57 (26.5)	9 (36.0)	3 (23.1)	45 (25.4)	2.821
Neurology clinics	168 (78.1)	16 (64.0)§	4 (30.9)‡	148 (83.6)	23.11†
Diagnosis					10.77*
Alzheimer's disease	80 (37.2)	9 (36.0)	0 (0.0)	71 (40.1)	
Vascular dementia	117 (54.4)	15 (60.0)	10 (76.9)‡	92 (52.0)	
Mixed dementia	18 (8.4)	1 (4.0)	3 (23.1)	14 (7.9)	
Severity					6.40
Unknown	32 (14.9)	3 (12.0)	0 (0.0)	29 (16.4)	
Mild to moderate	94 (43.7)	12 (48.0)	7 (53.8)	75 (42.4)	
Moderate to severe	79 (36.7)	9 (36.6)	4 (30.9)	66 (37.3)	
Severe	10 (4.7)	1 (4.0)	2 (15.4)	7 (4.0)	
Concurrent medications					
Valproate	10 (4.7)	0 (0.0)	0 (0.0)	10 (5.6)	2.25
Antidepressants	52 (24.5)	8 (32.0)	3 (23.1)	41 (23.2)	0.94
Benzodiazepines	18 (8.4)	2 (8.0)	2 (15.4)	14 (7.9)	0.89
Cholinesterase inhibitors	46 (21.4)	4 (16.0)	0 (0.0)	42 (23.7)	4.54
Memantine	8 (3.7)	0 (0.0)	0 (0.0)	8 (4.5)	0.41

*$p < 0.05$, †$p < 0.01$: comparisons among the 3 antipsychotic groups; ‡$p < 0.01$, §$p < 0.05$: vs. quetiapine group.

The other two patients taking haloperidol and zotepine were excluded due to very small group size. There were significant differences in age, diagnosis, and distribution of clinics among the three groups.

Severity coded by methods defined in this study had a fair correlation with BEHAVE-AD scores (Kendall's tau b correlation coefficient = 0.566, $p = 0.001$), supporting an acceptable accuracy of data coding. Table 2 shows the optimal dose, time to stable state, duration of stable state and total duration of target antipsychotic treatment. Although the definition of stable state only requires a duration of at least 4 weeks, the actual duration of "stable state" usually is much longer than 4 weeks. For example, the range of stable state for the 215 patients was 42 to 2703 days, with 99.5% of the patients having a stable state of ≥8 weeks, 90.2% ≥12 weeks and 82.8% ≥16 weeks. This means that the majority of this sample had been stabilized for 3 to 4 months, rather than 1 month only. The effectiveness of the antipsychotic agents was also reflected by a long median and mean duration of stable state (median 245 days, mean 374 days).

For the whole sample, there was not only a long duration of stable state, but also a long total duration of target antipsychotic treatment (median 525 days, mean 707 days; Table 2). The median time to stable state was 0 days for the whole group, indicating >50% of the patients could get the

Table 2 Optimal dose, time to stable state, duration of stable state and total duration of antipsychotic treatment of the three antipsychotic groups.

	Total ($N = 215$)		Risperidone ($N = 25$)		Sulpiride ($N = 13$)		Quetiapine ($N = 177$)		H
	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	
Optimal dose (mg/d)	—	—	1.0	1.0 (0.5)	100.0	126.9 (104.8)	25.0	43.8 (56.0)	
Time to stable state (d)	0	21 (47)	0	5 (13)§	28	39 (40)	0	22 (50)§	11.973†
Duration of stable state (d)	245	374 (385)	168	215 (157)	211	398 (705)	266	394 (373)‡	8.156*
Total duration of target antipsychotic treatment (d)	525	707 (587)	238	488 (566)	390	792 (978)	611	732 (550)‡	8.237*

*$p < 0.05$, †$p < 0.01$: comparisons among the 3 antipsychotic groups (Kruskal–Wallis test); §$p < 0.01$: vs. sulpiride group (Mann–Whitney test); ‡$p < 0.01$: vs. risperidone (Mann–Whitney test).

optimal dose right from the beginning. There were significant differences on time to stable state ($p < 0.01$), duration of stable state ($p < 0.05$) and total duration of antipsychotic treatment ($p < 0.05$) among the three groups. *Post-hoc* analysis found that sulpiride group had significantly longer time to stable state than the other two groups, while the risperidone group had significantly shorter duration of stable state and total duration of antipsychotic treatment than the quetiapine group (Table 2).

For a total of 176 patients whose reasons for leaving stable state were well recorded, Table 3 shows the respective duration of stable state and total duration of antipsychotic treatment related to different reasons. Even for those who had achieved satisfactory condition, the median duration of stable state was longer than 3 months, and the median total duration of antipsychotic treatment was >1 year. The cohort effects of prescription behaviors in the quetiapine group are shown in Table 4. Cohort 3 had significantly lower dose and shorter duration of quetiapine treatment than Cohort 1 or Cohort 2 ($p < 0.01$). When Cohort 3 was compared to Cohort 2, the reduction for optimal dose was 47.7% [= (64.2 − 33.6)/64.2], for duration of stable state 24.2%, and for total duration of antipsychotic treatment 18.7%.

Discussion

We aimed to study the optimal dose and duration of antipsychotic treatment for dementia-related agitation and/or psychosis, and to examine whether these prescription behaviors changed or not after the FDA warnings in 2003 and 2005. The main findings from this particular sample were: (1) the optimal doses of antipsychotics were similar to those of western reports, except that the dose of quetiapine was slightly lower; (2) the sulpiride group had longest time to reach stable state, while the risperidone group had the shortest duration of stable state and total duration of antipsychotic treatment; and (3) overall, the duration of stable state and total duration of antipsychotic treatment were long, but the dose and duration of antipsychotic treatment decreased significantly after 2005.

In addition to total duration of antipsychotic treatment, we also defined "stable state" and "optimal dose" in order to investigate physicians' prescribing behaviors in a clearer manner. Similar definitions have been applied to schizophrenia patients to study the optimal dose of antipsychotics, which yielded important findings for Taiwanese population when compared to Caucasian analogs.[19,21] To make the definition more valid, we further required that the stable period should be verified by two clinical visits at adequate interval and improvements should be documented. The findings that 99.5% of the 215 patients had a stable state of ≥8 weeks, 90.2% ≥12 weeks and a long median (mean) duration of stable state (≥245 days) support the efficacy of optimal dose and clinical validity of "stable state" in our study. In theory, by applying these inclusion criteria, we identified a group of demented patients who were responders to antipsychotic treatment. By adopting the concept of "duration of stable state", "reasons for leaving stable state", and "total duration of antipsychotic treatment" together, we can investigate physicians' prescribing behaviors under different situations in a better manner than previous studies, which usually reported total duration of antipsychotic treatment only.

According to previous clinical trials, target doses of antipsychotic agents for agitation and/or psychosis in patients with AD were recommended as 0.5 to 1.5 mg/day for risperidone and 50 to 200 mg/day for quetiapine.[22] In a recent rater-blinded head-to-head randomized study comparing both antipsychotic agents in treating behavioral symptoms of dementia, Rainer et al reported that the drugs were equally effective, and the mean dose was 0.9 mg/day for risperidone and 77 mg/day for quetiapine.[23] In the CATIE-AD study, the mean quetiapine dose (57.0 mg/day) was higher than that in our study (37.5 mg/day for AD patients).[24] Overall, the optimal dose of risperidone in our study was similar to the reported doses, but the mean quetiapine dose was somewhat lower. Several factors may account for the differences. First, our recruited subjects were outpatients rather than institutionalized or hospitalized patients, whose conditions are usually severer and thus require higher doses of treatment. Second, patients with poor response to antipsychotic agents were not included in our study, but this group of patients constituted a portion of subjects in clinical trials and was usually prescribed of higher doses. Third, most of our patients had mild to moderate degree of symptom severity, in contrast to moderate to severe degree of severity in the CATIE-AD study, although both studies recruited outpatients only.

The median time to stable state of all 215 patients was 0 days indicates that at least 50% of the patients could be stabilized by a dose not larger than recommended

Table 3 Duration of stable state related to different reasons for leaving stable state.

Reason for leaving stable state	*N* (%)	Duration of stable state		Total duration of target antipsychotic treatment	
		Median	Mean (SD)	Median	Mean (SD)
Loss of efficacy (d)	71 (40.3)	245	346 (291)	716	858 (583)
Achieving satisfactory condition (d)	36 (20.5)	172	244 (193)	381	634 (585)
Adverse reactions (d)	29 (16.5)	218	329 (300)	582	666 (478)
Loss of follow-up (d)	28 (15.9)	121	313 (515)	200	592 (753)
Death or new medical condition (d)	4 (2.3)	186	412 (493)	702	688 (586)
Other reason (d)	8 (4.5)	349	461 (281)	547	682 (575)
Total (d)	176 (100.0)	245	374 (385)	589	726 (600)

Table 4 Comparisons of optimal dose, duration of stable state, and total duration of antipsychotic treatment among three quetiapine cohorts.

	Cohort 1 ($N = 21$)		Cohort 2 ($N = 43$)		Cohort 3 ($N = 40$)		H
	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	
Optimal dose (mg/d)	50.0	71.4 (86.3)†	25.0	64.2 (77.7)†	25.0	33.6 (34.0)	11.98*
Duration of stable state (d)	266	364 (242)	513	472 (257)	349	358 (224)	4.69
Total duration of target antipsychotic treatment (d)	730	683 (127)†	730	668 (148)†	719	543 (235)	12.47*

Cohort 1: starting points before April 30, 2003; Cohort 2: starting points between May 1, 2003 and April 30, 2005; Cohort 3: starting points between May 1, 2005 and April 30, 2006. *$p < 0.01$: comparison among the 3 groups (Kruskal–Wallis test); $^{\dagger}p < 0.01$: vs. cohort 3 (Mann–Whitney test).

antipsychotic doses right from the beginning. The median time to stable state was 0 days for both risperidone and quetiapine group, but 28 days in the sulpiride group. One possible explanation is that sulpiride is not commonly used by physicians, and virtually not available in many western countries, so no recommended dose exists in most guidelines. The physicians had to titrate the dose in order to reach stable state. In contrast, the risperidone group had the shortest total duration of antipsychotic treatment and duration of stable state. Several factors may account for this finding. First, risperidone may be relatively more effective in the treatment of agitation/psychosis. This is supported by recent meta-analyses.[12,13] Second, risperidone may be associated with significant adverse effects that limit its continuous use.[12,13] Third, risperidone was the first antipsychotic agent to get an FDA warning and physicians are more aware of its adverse effects.[14]

The overall long duration of antipsychotic treatment was also reflected by long duration of treatment related to different reasons for leaving stable state (Table 3). Even for the reason of "achieving satisfactory condition", the duration of stable state was long (median: 172 days, mean 244 days), and the total duration of antipsychotic treatment was even longer (median up to 1 year, mean up to 1.7 years). The duration of treatment for patients leaving stable state due to other reasons was usually longer than that for patients leaving stable state due to "achieving satisfactory condition". The good news is that the dose and duration of antipsychotic treatment decreased significantly after the FDA warning in 2005, as shown in Table 4. For a 2-year observation, compared to Cohort 2, Cohort 3 had a mean dose reduction of 47.7% and a mean total duration reduction of 18.7%. The changes are significant, although the median and mean total duration of treatment in cohort 3 were still 719 days and 543 days within a 730-day observation period. Our preliminary study using a national claim dataset from 2001 to 2007 also found that the prescription duration of antipsychotics in patients with dementia was still long and the prescribed dose did not decrease significantly.[25]

Although the morbidity and mortality risks associated with antipsychotic treatment occur shortly within 30 days of prescription,[26] a placebo-controlled study found that the differences in mortality between the continuation group and placebo group were even more pronounced 24 and 36 months later.[27] With increasing evidence of the risks of antipsychotics in elderly dementia, practice guidelines generally recommended regular review of the benefits and harms of treatment and frequent trials of dose reduction or discontinuation after a period of time of stabilization, for example, no more than 12 weeks.[11,28–30]

Our study could not address why physicians maintained antipsychotic agents long without trials of changing the dose. There were several possible reasons, for example, the suboptimal therapeutic effects of antipsychotics, symptom aggravation after tapering the dose,[31] the inefficacy or unavailability of nonpharmacological intervention, inadequate family support, the favorable sedative effects of antipsychotics for insomnia, and the differential risk associated with different antipsychotics. Our study found that quetiapine was the most frequently prescribed and associated with longest median total duration of treatment. Low dose quetiapine has a good hypnotic effect and very few extrapyramidal side effects, which help agitated patients sleep better and decrease the caregiver burden. Several physicians admitted that they prescribed low dose quetiapine because of this reason (personal communication). A recent population-based cohort study found that, compared with risperidone, users of haloperidol had an increased risk of mortality and users of quetiapine a decreased risk.[32] Future studies are needed to find factors that predispose to continuous use of antipsychotics, and new treatment with better efficacy and favorable side effect profile should be developed.

There are several limitations of our study. First, it was a retrospective study and data were collected from medical charts. Documentation in charts might be inadequate or incomplete. Symptom profile, clinical severity, and treatment response had to be inferred. Information about adherence to treatment was often unavailable. Second, only the database of one hospital was studied. Therefore the results may not be generalizable. Finally, only responders of antipsychotic agents were studied, so the results could not be generalized to all demented patients with agitation or psychosis.

In conclusion, our study suggests that the mean dose and duration of antipsychotic treatment decreased significantly after the FDA warning in 2005 in this national medical center, but the duration remains long. This has important clinical implication because antipsychotics are associated with significant morbidity and mortality risks. Regular review of prescriptions and early trials of withdrawing antipsychotic agents should be advocated.

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